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COMPLEMENT ACTIVITY INHIBITOR

(Hotai Kassei Yokuseizai)

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SPECIFICATION

(54) Title of the Invention

Complement Activity Inhibitor

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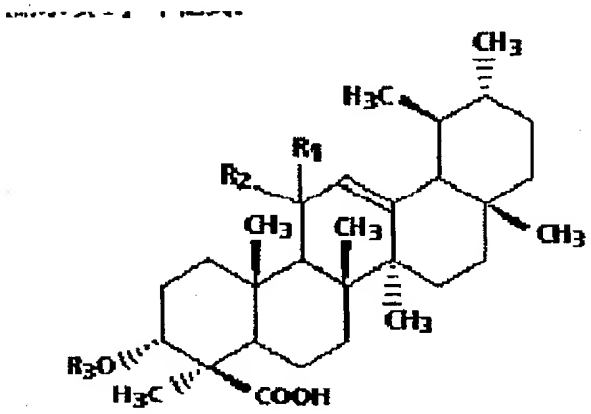
[Claims]

[Claim 1] A complement activity inhibitor which takes a compound expressed by the following formula I



(where R_1 and R_2 represent hydrogen atoms or α-hydroxyl group or both R_1 and R_2 represent an oxygen atom, and R_3 represents a hydrogen atom or an acetyl group in Formula I.) or a pharmacologically allowable salt thereof as active ingredient.

[Detailed Description of the Invention]

[1] Numbers in margin indicate pagination in foreign text.

[0001]

[Field of Industrial Application] The present invention relates a complement activity inhibitor with ∃-boswellic acid and ∃-boswellic acid derivatives such as 11-keto-∃-boswellic acid, 11-α-hydroxy-∃-boswellic acid, etc. as active ingredient.

[0002]

[Prior Art] In the immune mechanism of living bodies, complements are a group of about 20 proteins having an important function in reactions for removing extrinsic foreign bodies and playing their roles in a subtle balance. If the complements are activated, their constituents are said to become chemical mediators and cause various physiological actions. It has been known that if the balance is disordered at this time, various abnormal pathoses, for example, autoimmunity diseases such as general erythematodes, chronic rheumatoid arthritis, etc. manifest.

[0003] Besides general disturbance caused by heterologous blood transfusion or inflammations caused by pneumococcus, more recently, there is such an opinion that psoriasis also relates to the abnormality of complements.

[0004] It is the present situation that efficient drugs which are fully satisfactory for the diseases as described above

have not been known so far. Anti-complement activity inhibitors are considered useful in the therapy of these diseases caused by excessive activation of the complements.

[0005] Recently, such an activity has been found in polysaccharides of some constituents of crude drugs, but the polysaccharides are generally mixtures and are hard to be specified as medicines, thus the development is difficult.

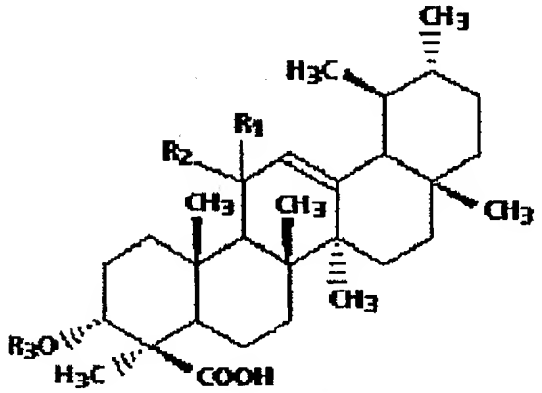
[0006]

[Problem to Be Solved by the Invention] Wagner of West Germany discovered a strong anti-complement activity in a mixture of α- and ∃-boswellic acids being constituents of a crude drug - mastic which has been used as fumet and antiphlogistic/ analgetic from the old [H. Wagner, *Planta Medica*, **55**, 235 (1989)], but the separation of this mixture was extremely difficult, and which substance has true activity was unclear. Accordingly, it was considered to enable the development of new anti-inflammatory agents against autoimmunity diseases based on the mechanism of inhibiting abnormal activation of complements by solving the problem.

[0007] The inventors repeated earnest studies which should solve the above problem, consequently they were successful in the separation of α- and ∃-boswellic acids and discovered that only ∃-boswellic acid had the activity and the same activity was

also found in its salts such as sodium salt, etc. and boswellic acid derivatives such as 11-keto-∃-boswellic acid, 11-α-hydroxy-∃-boswellic acid, etc., thus came to accomplish the present invention.

[0008] Namely, the present invention is a complement activity inhibitor which takes a compound expressed by the following formula I



(where R_1 and R_2 represent hydrogen atoms or α-hydroxyl group or both R_1 and R_2 represent an oxygen atom, and R_3 represents a hydrogen atom or an acetyl group in Formula I.) or a pharmacologically allowable salt thereof as active ingredient.

[0009] The compounds expressed by the Formula I called compounds of the formula below.

[0010] In the compounds of the formula, a compound in which R_1 and R_2 are hydrogen atoms and R_3 is an acetyl is ∃-boswellic acid, the authors carried out its separation from α-boswellic

acid and first confirmed that it is the main body of anti-complement activity, and other compounds of the formula are also known substances given in the literature, but their anti-complement activity is not clarified, and the activity is first clarified by the authors.

[0011] For example, the compounds of the formula can be obtained as follows.

[0012] Namely, mastic (a resin exudated from the trunk of *Boswellia carteri*, *Boswellia bhaw-dajiana*, *Boswellia neglecta*, etc.) or Indian mastic (*Boswellia serrata*) is extracted by heating it to a temperature below the boiling point of employed solvent with a solvent or a mixed solvent of two or more selected from organic solvents, e. g., hydrocarbons such as petroleum ether, pentane, hexane, cyclohexane, etc., lower alcohols such as methanol, ethanol, propanol, etc., acetone, methyl ethyl ketone, methylene chloride, chloroform, ethyl acetate, etc. or extracted by ultrasonic wave from 0°C to room temperature to obtain an extract.

[0013] This extract was fractionated to give fractions by removing the solvents and applying it to column chromatography or

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high-speed liquid chromatography once or several times. At this time, solvents, e. g., hydrocarbons such as petroleum ether,

pentane, hexane, cyclohexane, etc. can be used separately or by mixing with solvents such as acetone, ethyl acetate, chloroform, methylene chloride, tetrahydrofuran, alcohols, etc. as eluting solvents.

[0014] The compounds of the formula are obtained by further recrystallizing the fractions thus obtained or by applying them to high-speed liquid chromatography with a reversed-phase gel such as ODS silica gel, porous polymer gel, etc. as adsorbent, to elute/fractionate fractions with methanol, tetrahydrofuran, acetonitrile, aqueous solvent and then recrystallization.

[0015] When a compound having an ester bond such as acetic acid, etc. is contained in the fractions obtained as described above, the compounds of the formula can be obtained by commonly-used alkaline hydrolysis.

[0016] As solvents for the recrystallization, water, lower alcohols, acetone, ethyl acetate, tetrahydrofuran, petroleum ether, pentane, hexane, cyclohexane, methylene chloride, chloroform, etc. may be used separately or by mixing two or more of them.

[0017] Next, specific examples of preparing the compounds of the formula are shown.

[0018] [Specific Example 1]

A nearly 1:1 mixture of acetates of α-boswellic acid and ∃-boswellic acid was obtained by applying 117 g of a petroleum ether extract of mastic to 1 kg of a silica gel column chromatography, eluting with a hexane/acetone solvent and then further purifying the 5th fraction by elution with an ODS reversed-phase gel (Fuji-Gel Q-3) and a methanol/water solvent. The mixture was crystallized from a hexane/acetone mixed solvent to obtain 873 mg of a colorless crystalline substance. This mixture was separated by a preparative HPLC column [D-ODS-10 (YMC, solvent; THF : CH_3CN : H_2O = 3:12:1, flow rate; 3 mL/min)]. 220 mg of α-boswellic acid acetate and 280 mg of ∃-boswellic acid acetate (R_1 and R_2 are hydrogen atoms and R_3 is an acetyl in Formula I) having the following physicochemical properties were obtained by removing the solvents of a fraction eluted at R_t of about 115 min and a fraction eluted at R_t of about 125 min.

[0019] α-Boswellic acid acetate (recrystallized from methanol, colorless needle crystal)

m.p. 218 - 219°C

$[\alpha]_D$ = +66.1° (c = 0.3, $CHCl_3$)

mass spectrum

EI-MS m/z: 498 [M^+], 218, 203

IR absorption spectrum IR_{max} cm^{-1}:

2972, 2944, 2860, 1744,

1730, 1705, 1242

proton NMR spectrum (* ppm in $CDCl_3$):

0.84, 0.87, 0.87, 0.90

1.01, 1.19, 1.12 (each 3H, s)

2.09 (3H, s), 5.20 (1H, t, J = 3.4 Hz),

5.30 (1H, t, J = 2.5 Hz)

[0020] ∃-Boswellic acid acetate (recrystallized from methanol, colorless needle crystal)

m.p. 227 - 228°C

$[\alpha]_D$ = +62.3° (c = 0.3, $CHCl_3$)

mass spectrum

EI-MS m/z: 498 [M^+], 218, 203

IR absorption spectrum IR_{max} cm^{-1}:

2976, 2920, 2860, 1746,

1730, 1702, 1240

proton NMR spectrum (* ppm in $CDCl_3$):

0.80 (3H, d, J = 6.3 Hz), 0.81 (3H, s)

0.91 (3H, s), 0.93 (3H, t, J = 6.1 Hz),

1.05, 1.12, 1.25 (each 3H, s)

2.10 (3H, s), 5.15 (1H, t, J = 3.5 Hz)

5.31 (1H, t, J = 2.5 Hz)

[0021] [Specific Example 2]

400 mg of ∃-boswellic acid acetate obtained in Specific Example 1 was dissolved in 25 mL of a 5% potassium hydroxide/ methanol and refluxed for 8 hr on a water bath, then 25 mL of 2 N hydrochloric acid was added to the reaction solution, and then the mixture was extracted three times with ether. The ether layers were put together and washed with a saturated aqueous table salt solution, then dried over anhydrous magnesium sulfate and the solvent was removed. 288 mg of ∃-boswellic acid (R_1, R_2 and R_3 are hydrogen atoms) having the following physicochemical properties was obtained as a white crystalline substance by purifying the residue with a preparative HPLC (D-ODS-10 column, THF : CH_3CN : H_2O = 3:12:1) and then recrystallizing it from hexane-acetone.

[0022] m.p. 236 - 238°C

$[\alpha]_D$ = +100.7° (c = 0.3, $CHCl_3$)

mass spectrum

EI-MS m/z: 456 [M^+], 441, 238

218, 203

IR absorption spectrum IR_{max} cm^{-1}:

3440, 2944, 1696

proton NMR spectrum (* ppm in $CDCl_3$):

0.79 (3H, d, J = 5.9 Hz),

0.81, 0.90 (each 3H, s)

0.92 (3H, d, J = 6.1 Hz),

1.04, 1.09, 1.35 (each 3H, s)

4.08 (1H, t, J = 2.7 Hz)

5.14 (1H, t, J = 3.6 Hz)

[0023] [Specific Example 3]

A white powder sodium ∃-boswellate having the following physicochemical properties was obtained by taking 15 mg of the ∃-boswellic acid obtained in Specific Example 2, well shaking and dissolving it in 3 mL of 0.05 M sodium hydroxide/methanol, concentrating it under reduced pressure to an extent of no dry-out and then adding ether thereto.

[0024] m.p. > 290°C

$[\alpha]_D$ = +51.4° (c = 0.2, MeOH)

IR absorption spectrum IR_{max} cm^{-1}:

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3432, 1634, 1552, 1348, 880

[0025] [Specific Example 4]

24.0 g and 27.5 g of extracts were obtained by crushing 100 g of Indian mastic, extracting it twice with 2 L of petroleum ether, further extracting it with 2 L of chloroform at room temperature, and then concentrating the extracts under reduced pressure to remove the solvents, respectively. 10 g of the chloroform extract of mastic was applied to 300 g of a silica gel

column chromatography, premixed with hexane and 2 - 30% of acetone in order and finally eluted with acetone only to fractionate the extract into 13 fractions. 1.89 g of a mixture of the 6th and 7th fractions was applied to 57 g of a silica gel column chromatography and then eluted with hexane/ethyl acetate = 4:1. 23.1 mg of a colorless prism crystal 11-keto-β-boswellic acid-3-O-acetate (both R_1 and R_2 become an oxygen atom and R_3 is an acetyl in Formula I) having the following physicochemical properties shown below was obtained by further repeatedly purifying this 5th fraction with a mixed solvent of hexane/ethyl acetate = 5:1 to obtain a substance absorbing UV ray and then recrystallizing it from hexane/acetone.

[0026] m.p. 270 - 276°C

$[\alpha]_D$ = +77.5° (c = 0.44, $CHCl_3$)

mass spectrum

EI-MS m/z:

512 [M^+], 273 (base peak), 232

high-resolution EI-MS m/z:

calcd. 512.3501 $C_{32}H_{48}O_5$

found 512.3506

UV absorption spectrum UV_{max} nm(ε): 252 (11200)

IR absorption spectrum IR_{max} cm^{-1}:

3300 - 2500, 1730, 1695

1650, 1615, 1250

proton NMR spectrum (* ppm in $CDCl_3$):

0.80 (3H, d, J = 6.2 Hz), 0.83 (3H, s)

0.95 (3H, br.s)

1.15, 1.20, 1.24, 1.35 (each 3H, s)

2.10 (3H, s), 2.41 (1H, s)

5.31 (1H, br.s), 5.56 (1H, s)

[0027] [Specific Example 5]

500 mg of 11-keto-∃-boswellic acid 3-O-acetate obtained in Specific Example 4 was dissolved in 25 mL of a 5% potassium hydroxide/methanol and thermally refluxed for 5.5 hr on a water bath and cooled, then the reaction solution was diluted with 100 mL of water, acidified with hydrochloric acid and a separated white precipitate was extracted three times with 100 mL of ether each. 511 mg of a colorless needle crystal 11-keto-∃-boswellic acid (both R_1 and R_2 become an oxygen atom and R_3 is a hydrogen atom in Formula I) having the physicochemical properties shown below was obtained by putting the extracts together, washed it twice with saturated table salt solution, drying it over anhydrous magnesium sulfate and then removing the solvent.

[0028] m.p. 192 - 193°C

$[\alpha]_D$ = +131° (c = 1.0, $CHCl_3$)

mass spectrum

EI-MS m/z: 470 [M^+], 455, 273, 232

high-resolution EI-MS m/z:

calcd. 470.3391 $C_{30}H_{46}O_4$

found 470.3400

UV absorption spectrum UV_{max} nm(ε): 250 (11400)

IR absorption spectrum IR_{max} cm^{-1}:

3500 - 2400, 1695, 1650, 1615

proton NMR spectrum (* ppm in $CDCl_3$):

0.79 (3H, d, J = 6.2 Hz)

0.82 (3H, d, J = 5.6 Hz)

0.95, 1.13, 1.19

1.31, 1.35 (each 3H, s)

2.43 (1H, s), 4.08 (1H, br.s)

5.55 (1H, s)

[0029] [Specific Example 6]

The 8th fraction successive to the fraction giving the compound obtained by Specific Example 4 contained a nearly single compound and was recrystallized from hexane/acetone to obtain 176.4 mg of a colorless needle crystal. 69 mg of the same substance was obtained as a colorless needle crystal by applying 349 mg of a mother liquor to 10.5 g of a silica column chromatography again, eluting it with 4:1 - 2:1 hexane/ethyl acetate, fractionating into 6 fractions and then recrystallizing

the 2nd and 3rd fractions from hexane/acetone. They gave 11-α-hydroxy-boswellic acid-3-O-acetate (both R_1 and R_2 become an oxygen atom and R_3 is an acetyl in Formula I) having the physicochemical properties shown below.

[0030] m.p. 160 - 166°C

$[\alpha]_D$ = +11.3° (c = 0.21, $CHCl_3$)

mass spectrum

EI-MS m/z: 514 [M^+], 496, 234 (base peak)

high-resolution EI-MS m/z:

calcd. 514.3658 $C_{32}H_{50}O_5$

found 514.3680

IR absorption spectrum IR_{max} cm^{-1}:

3640, 3300 - 2500, 1750, 1730, 1280

proton NMR spectrum (* ppm in $CDCl_3$):

0.86 (3H, d, J = 6 Hz)

0.88, 0.92, 1.07, 1.11

1.22, 1.25 (each 3H, s)

1.63 (1H, d, J = 8.8 Hz)

2.10 (3H, s)

4.27 (1H, dd, J = 9.2, 3.3 Hz)

5.18 (1H, d, J = 2.9 Hz)

5.30 (1H, br.s)

[0031] [Specific Example 7]

50.3 mg of 11-α-hydroxy-∃-boswellic acid-3-O-acetate obtained in Specific Example 6 was taken, dissolved in 6 mL of a 5% potassium hydroxide/methanol and thermally refluxed for 6 hr on a water bath, cooled, and then methanol was removed under reduced

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pressure. The residue was dissolved in 20 mL of ether, washed with 2N hydrochloric acid, saturated aqueous sodium bicarbonate and aqueous table salt solution, 15 mL for each, and then dried over anhydrous sodium sulfate. 26.3 mg of a colorless crystal 11-α-hydroxy-∃-boswellic acid (R_1 and R_3 are hydrogen atoms, and R_2 is α-hydroxyl in Formula I) having the physicochemical properties shown below was obtained by removing the solvent under reduced pressure and recrystallizing it from hexane/ethanol).

[0032] m.p. 171 - 178°C

$[\alpha]_D$ = +63.9° (c = 0.33, $CHCl_3$)

mass spectrum

EI-MS m/z: 472 [M^+], 454 (M^+-H_2O)

high-resolution EI-MS m/z:

calcd. 472.3552 $C_{30}H_{48}O_4$

found 472.3556

IR absorption spectrum IR_{max} cm^{-1}:

3690, 3000 - 2500, 1720

proton NMR spectrum (* ppm in $CDCl_3$):

0.81 (3H, s), 0.85 (3H, d, J = 5.5 Hz)

0.93 (3H, br.s)

1.07, 1.10, 1.18, 1.37 (each 3H, s)

1.61 (1H, d, J = 8.8 Hz)

4.08 (1H, br.s)

4.26 (1H, dd, J = 9.2, 3.3 Hz)

5.18 (1H, d, J = 2.9 Hz)

[0033] [Reference Example]

25 mL of a 5% potassium hydroxide/methanol was added to 420 mg of α-boswellic acid acetate obtained in Specific Example 1, refluxed for 8 hr on a water bath, then 25 mL of 2 N hydrochloric acid was added to the reaction solution, and a separated white precipitate was extracted with ether. The ether layer was washed with saturated table salt solution, dried over anhydrous magnesium sulfate, and then the solvent was removed under reduced pressure to obtain a white powder. 312 mg of α-boswellic acid having the physicochemical properties was obtained as a colorless flaky crystal by recrystallizing it from methanol.

[0032] m.p. 140/190 - 230°C (double m.p.)

$[\alpha]_D$ = +108.7° (c = 0.3, $CHCl_3$)

EI-MS m/z:

456 [M^+], 441, 259, 238, 218, 203

IR absorption spectrum IR_{max} cm^{-1}:

3400, 2944, 2856, 1720

proton NMR spectrum (* ppm in $CDCl_3$):

0.84, 0.87, 0.87, 0.89

1.00, 1.15, 1.35 (each 3H, s)

4.08 (1H, t, J = 2.6 Hz)

5.20 (1H, t, J = 3.4 Hz)

[0035] Subsequently, the superior anti-complement activity of compounds of the formula and their usefulness as complement activity inhibitor are illustrated by giving test examples.

[0036] [Test Example 1]

Measurements of the anti-complement activity were carried out by making Meyer's method to a 1/5 scale (Meyer, M. M. *Experimental Immunochemistry*, 2nd, p. 133). Namely, rabbit-anti sheep erythrocyte was used as antibody, sheep erythrocyte was used as antigen and CPD-stored human plasma was used as complement source. The compounds of the formula are sparsely dissolved in water, therefore they were dissolved in dimethyl sulfoxide (DMSO) so as to become 10 mM and then added into a gelatin-Bernard buffer so that the final concentration became 50 :m. The diluted plasma was changed to 0.25, 0.3, 0.35, 0.4, 0.5, 0.7 mL, the sensitized sheep erythrocyte was mixed with distilled water and osmosized at 37°C for 2 hr, then the reaction

was stopped by ice cooling, centrifuged for 5 min at 2,500 rpm, and the absorbance of supernatant at 414 nm was measured at the concentrations of diluted plasma. 1 :L of DMSO was taken as a control. The results are shown below. CB represents mechanical hemolysis in tables.

[0037] Table 1 (Anti-complement activity of compounds obtained in specific examples)

Amount of Diluted Plasma (mL)	Control	Compound Obtained in Specific Example 2	Compound Obtained in Specific Example 3	Compound Obtained in Specific Example 5	Compound Obtained in Specific Example 7	Compound Obtained in Reference Example
0.25	0.039	0.012	0.007	0.012	0.024	0.077
0.30	0.085	0.030	0.015	0.048	0.045	0.093
0.35	0.128	0.049	0.023	0.054	0.080	0.131
0.40	0.191	0.081	0.033	0.079	0.098	0.168
0.50	0.290	0.089	0.031	0.154	0.105	0.243
0.70	0.532	0.272	0.185	0.394	0.447	0.463
CB	0.008	0.014	0.005	0.010	0.003	0.033

[0038] Table 2 (Concentration dependence of compounds obtained in Specific Example 2)

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Amount of Diluted Plasma (mL)	Control	50 :M	25 :M	12.5 :M	5 :M
0.23	0.009	0.020	0.013	0.006	0.011
0.30	0.009	0.008	0.018	0.045	0.051
0.35	0.067	0.014	0.054	0.082	0.107
0.40	0.207	0.121	0.147	0.175	0.231
0.50	0.293	0.173	0.237	0.307	0.354
0.70	0.471	0.381	0.418	0.455	0.417
CB	0.009	0.020	0.013	0.006	0.011

[0039] Table 3 (Concentration dependence of compounds obtained in Specific example 3)

Amount of Diluted Plasma (mL)	Control	50 :M	25 :M	12.5 :M	5 :M
0.25	0.052	0.007	0.021	0.039	0.033
0.30	0.009	0.015	0.036	0.062	0.060
0.35	0.135	0.023	0.063	0.091	0.105
0.40	0.191	0.033	0.092	0.121	0.179
0.50	0.309	0.031	0.163	0.215	0.256
0.70	0.527	0.185	0.361	0.445	0.483
CB	0.004	0.005	0.008	0.005	0.011

[0040] Table 4 (Concentration dependence of compounds obtained in Specific Example 5)

Amount of Diluted Plasma (mL)	Control	50 :M	25 :M	12.5 :M	5 :M
0.25	0.090	0.074	0.022	0.015	0.016
0.30	0.139	0.100	0.136	0.097	0.087
0.35	0.235	0.168	0.192	0.152	0.185
0.40	0.283	0.231	0.241	0.228	0.251
0.50	0.411	0.337	0.362	0.343	0.382
0.70	0.472	0.470	0.461	0.467	0.469
CB	0.012	0.017	0.022	0.015	0.016

[0041] As is evident from these results, it was proved that the compounds of the formula have the anti-complement activity.

[0042] Next, the doses and preparations of the compounds of the formula are illustrated.

[0043] The compounds of the formula can be administered into animals or mankind as they are or along with conventional carriers for preparations. The forms of administration are not

specially restricted and are used by proper selection according to demand, oral drugs such as tablets, capsules, granules, fine grains, powders, etc. and parenteral drugs such as injections, suppositories, etc. are given.

[0044] To display expected effects as oral drugs, the dose depends on age, body weight of patients and the degree of diseases, usually, 10 - 3 g as weight of the compounds in several doses a day is thought to be suitable for adults.

[0045] The oral drugs are prepared according to ordinary methods with, e. g., starch, lactose, white sugar, mannite, carboxymethyl cellulose, corn starch, inorganic salts, etc.

[0046] In addition to said vehicles, binder, disintegrate, surfactant, lubricant, fluidity improver, corrective, colorant, perfume, etc. can be properly used in these kinds of preparations. Respective specific examples are as shown below.

[0047] [Binders] Starch, dextrin, Arabic gum dust, gelatin, hydroxypropyl starch, methyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl cellulose, crystalline cellulose, ethyl cellulose, polyvinylpyrrolidone, macrogol.

[0048] [Disintegrants] Starch, hydroxypropyl starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxy-methyl cellulose, low-substituted hydroxypropyl cellulose.

[0049] [Surfactants] Sodium lauryl sulfate, soybean lecithin, sucrose fatty acid esters, polysorbate 80.

[0050] [Lubricants] Talc, waxes, hydrogenated vegetable oils, sucrose fatty acid esters, magnesium stearate, calcium stearate, aluminum stearate, polyethylene glycol.

[0051] [Fluidity improvers] Light anhydrous silicic acid, dry aluminum hydroxide gel, synthetic aluminum silicate, magnesium silicate.

[0052] Moreover, the compounds of the formula can also be administered as suspension, emulsion, syrup, elixir, etc., and corrective/flavoring agents, colorants in these various dose forms.

[0053] To display expected effects as parenteral drugs, the does depends on age, body weight of patients and the degree of diseases, usually, intravenous injection, intravenous instillation, subcutaneous injection, muscular injection, etc. of up to 5 - 500 mg as weight of the compounds are thought to be suitable for adults.

[0054] These parenteral drugs are prepared according to ordinary methods, and distilled water for injection, physiological saline, aqueous glucose solution, vegetable oil for injection, sesame oil, peanut oil, soybean oil, corn oil, propylene glycol, polyethylene glycol, etc. can be generally

used as diluents. Bactericide, antiseptic, stabilizer may also be added as necessary. From the viewpoint of stability, these parenteral drugs can also be prepared again from a frozen dry matter into a liquid preparation immediately before use by packing it into a vial, etc. then freezing it, and removing water by common freeze drying technique. Moreover, isotonic agent, stabilizer, antiseptic, indolentia agent, etc. may also be added.

[0055] As other parenteral drugs, external liquid preparations, coating agent such as ointment, etc., suppositories for rectal administration, etc. are given and prepared according to ordinary methods.

[0056] Next, the present invention is illustrated in more

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detail by giving actual examples, but the present invention is not limited thereto.

[0057] [Actual Example 1]

← Corn starch	44 g
↑ Crystalline cellulose	40 g
→ Calcium carboxymethyl cellulose	5 g
↓ Light anhydrous silicic acid	0.5 g
° Magnesium stearate	0.5 g

± Compound obtained in Specific Example 2	10 g
Total	100 g

← - ± were uniformly mixed according to the above formula and compression molded by a tabletting machine to obtain tablets of 200 mg per tablet. 20 mg per tablet of the compound obtained in Specific Example 2 is contained, and 5 - 15 tablets are administered in several doses per day per adult.

[0058] [Actual Example 2]

← Crystalline cellulose	84.5 g
↑ Magnesium stearate	0.5 g
→ Calcium carboxymethyl cellulose	5 g
± Compound obtained in Specific Example 3	10 g
Total	100 g

←, ↓ and a part of ↑ were uniformly mixed according to the above formula, then → and the balance of ↑ were added, mixed and compression molded by a tabletting machine to obtain tablets of 200 mg per tablet. 20 mg per tablet of the compound obtained in

Specific Example 3 is contained, and 5 - 15 tablets are administered in several doses per day per adult.

[0059] [Actual Example 3]

← Crystalline cellulose	49.5 g
↑ 10% Ethanol solution of hydroxypropyl cellulose	35 g
→ Calcium carboxymethyl cellulose	5 g
↓ Magnesium stearate	0.5 g
± Compound obtained in Specific Example 5	10 g
Total	100 g

←, ↑ and ° were uniformly mixed according to the above formula, kneaded by ordinary method, pelletized by extrusion pelletizer, dried and disintegrated, then → and ↓ were mixed and the mixture was compression molded by a tabletting machine to obtain tablets of 200 mg per tablet. 20 mg per tablet of the compound obtained in Specific Example 5 is contained, and 5 - 15 tablets are administered in several doses per day per adult.

[0060] [Actual Example 4]

← Corn starch	34.5 g

↑ Magnesium stearate	50 g
→ Calcium carboxymethyl cellulose	5 g
↓ Light anhydrous silicic acid	0.5 g
± Compound obtained in Specific Example 7	10 g
Total	100 g

← - ° were uniformly mixed according to the above formula, compression molded by a tabletting machine, then crushed by a crusher and sieved to obtain granules. 100 mg of the compound obtained in Specific Example 7 is contained in 1 g of this granule, and 1 - 3 g is administered in several doses per day per adult.

[0061] [Actual Example 5]

← Crystalline cellulose	55 g
↑ 10% Ethanol solution of hydroxypropyl cellulose	35 g
→ Compound obtained in Specific Example 2	10 g
Total	100 g

← - → were uniformly mixed according to the above formula and then kneaded. The mixture was pelletized by an extrusion pelletizer, dried and sieved to obtain granules. 100 mg of the compound obtained in Specific Example 2 is contained in 1 g of this granule, and 1 - 3 g is administered in several doses per day per adult.

[0062] [Actual Example 6]

← Corn starch	89.5 g
↑ Light anhydrous silicic acid	0.5 g
→ Compound obtained in Specific Example 3	10 g
Total	100 g

← - → were uniformly mixed according to the above formula, and 200 mg was packed in a No. 2 capsule. 20 mg of the compound obtained in Specific Example 3 is contained in one capsule of these capsules, and 5 - 15 capsules are administered in several doses per day per adult.

[0063] [Actual Example 7]

← Soybean oil	5 g
↑ Distilled water for injection	89.5 g

→ Soybean phosphatide	2.5 g
↓ Glycerin	2 g
° Compound obtained in Specific Example 5	1 g
Total	100 g

° was dissolved in ← and → according to the above formula, then a solution of ↑ and ↓ was added and emulsified to obtain an injection.